

# Trends and Perspectives of the Biological Prophylaxis of Silicosis

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Based on earlier paper in this journal, as well as on new data concerning factors predetermining individual susceptibility to silicosis, we propose a comprehensive system of recommendations aimed at increasing the working population's resistance against the harmful action of silica dust. These recommendations consider, on one hand, the criteria of possible selection for employment in dusty industries of individuals who do not possess characteristics making them especially sensitive to this harmful action (collective biological prophylaxis), and on the other hand, the influences that could diminish such sensitivity (individual biological prophylaxis). Some ethical and practical problems of the biological prophylaxis of occupational diseases and a mathematical approach to predicting its effectiveness are also discussed.

## Introduction

The main objective of the prophylaxis of any occupational disease is to completely exclude from the industrial environment the harmful factor that induces this disease (first of all, through radical changes of the technology), or, if this is impossible, at least to decrease the factor's intensity to such a level that it would not noticeably affect the health of even the most sensitive workers within the maximal working lifespan. However, one can consider in principle another possible objective: to decrease sensitivity (or to increase resistance) of a working population to such a degree so that even at some potentially harmful level, the probability of contracting the disease and/or its gravity would be brought down. If and when a technology cannot be radically changed, while the modern state of engineering makes the achievement of a completely safe exposure level very difficult or unreliable, this auxiliary trend of prophylaxis is of a special significance.

Prophylactic vaccination as a method of increasing the host's specific resistance to an ineradicable risk of a bacterial or viral infection may serve as an example of a measure which, not excluding the necessity of hygienic and epidemiological control of a disease, significantly enhances its effectiveness. Theory and practice of non-specific methods of increasing the host's resistance to diverse diseases (through physical culture, cold acclimatization and rationalization of nutrition and of lifestyle) have even more history. Theory and especially practice of a similar approach to the prophylaxis of occupational diseases are still in an embryonic state.

This field of research does not even have, as yet, a stable scientific terminology. We feel that "biological prophylaxis" is an adequate term as it makes clear that measures under consideration aim not at technology or the industrial environment but at sensitivity (resistance) of a human population that is under harmful exposure, this sensitivity and resistance being mainly biological categories. (Like any classification term this one is not unqualified, as biological prophylaxis is closely contiguous to problems of a social nature.)

Biological prophylaxis as defined above includes two different approaches aiming at the same goal. The principle of the first one is to diminish the probability of employment in a specific industry of persons whose susceptibility to occupational diseases inherent in that industry might be much higher than average. Thus the working subpopulation as a whole would be made less susceptible,

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and the prevalence of occupational diseases in it would decrease, i.e., the chief purpose of biological prophylaxis would be obtained. This variant of biological prophylaxis could be named collective or populational.

Another approach is based on finding and exerting such influences on the organism which, being harmless by themselves, could enhance the organism's resistance to the occupational harmful factor. Here belongs also a complete prevention of or at least restriction of some actual influences (both harmful and innocuous by themselves) which can enhance the host's sensitivity to some specific potentially injurious factor of the industrial environment. As the immediate object of such prophylactic measures is an individual (although they add up to the same increased resistance of a working subpopulation), this approach could be named "individual biological prophylaxis."

## Collective Biological Prophylaxis

The authors' experience focused on the study of silicosis, and therefore it is silicosis that is discussed in this overview. Many approaches to the problem of silicosis and the results obtained in the investigations might be applied to other pneumoconioses as well. However, the possibility of the collective biological prophylaxis of any occupational disease involves a certain problem of social ethics.

Samuels consistently maintains the priority of human values over considerations of gaining the maximum profits of an enterprise stating that it would be unethical "to mold man to the machine" (1).

We feel that such a polemical accentuation of the problem would be justified only if selection of the resistant (or elimination of the sensitive) individuals for employment in the harmful environment were openly or covertly proposed as an alternative to expense and effort directed toward improvement of working conditions, instead of regarding such selection (elimination) as a supplement to such expense and efforts. Besides, the specific method of conducting the selection is an internal matter of a country and depends on traditions of its society. It may be organized through the obligatory medical examination of each person applying for employment in certain industries, or a medical examination may be performed when demanded by the applicant. It may be regulated by special legal acts prohibiting the employment of individuals bearing certain unfavorable characteristics, or it may be only an unobligatory medical recommendation that the person seeking such employment should or should not take into consideration. Examples of law-enforced restrictions on employment are the prohibition of child labor in industry, which was first adopted in Great Britain in the 19th century, and women's underground work which is, as far as we know, forbidden in all member countries of the International Labor Organization. It would be really strange to see in these bans a violation of human rights.

The healthy worker's effect, well known to epidemiologists, testifies to the widespread operation of natural selection of those who are more resistant to adverse ef-

fects of different harmful occupational exposures. Some rational control of this natural process, making it more effective and less painful, seems quite reasonable and justified. Regardless of legal or other tools of such control, even if it were limited but to a physician's advice, in any case it should be based upon scientifically valid principles of medical occupational selection. One has to determine who should not be employed in certain industries before deciding how to prevent this employment.

## Screening of Individuals Susceptible to Silicosis: Age and Sex Selection

Proper screening and selection can be achieved only after one has considered the characteristics that determine an individual's predisposition to the occupational disease under consideration. The characteristics relevant to silicosis development have been discussed previously in this journal (2). Therefore, we shall continue the analysis of these characteristics only if important new results have been obtained in the meantime.

In particular, we have already referred in overview to our own as well as to other authors' data, both experimental and epidemiological, which testified to a greater predisposition of females to develop silicosis as compared with males (2). Later, the multifactorial analysis based on the mathematical theory of pattern recognition confirmed that in a silicafirebrick factory the female employee was one characteristic enhancing the probability of contracting this occupational disease (3).

The same method was used as a mathematical model for predicting the prophylactic effectiveness of biological prophylaxis in the proposed meaning of the term. For this purpose individuals described as a set of relevant features (in our investigation there were 15 of them (2)) were presented to the computer after only one of the features predisposing to silicosis had been eliminated or changed so as to become favorable. The computer, operating on the basis of previously elaborated discrimination rule, had to recognize again these individuals as those who would or would not contract silicosis. A proportion of workers who without such correction of an unfavorable feature had been recognized as predisposed to silicosis (and who had in fact contracted this disease) was recognized after the correction as those who would remain healthy. This proportion is used as a measure of prophylactic effect, which can be predicted for a real corrective influence on the working population (or on the individual). Thus, in that firebrick factory, such a substitution of male for female workers (with the other 14 features remaining the same) decreased the total number of silicosis cases by 25%.

A similar prophylactic effect is predicted by the model for nonadmittance of persons under 20 into the silica-brick industry. Young age at beginning "dusty" work was found both in this industry and in copper mines to be the most vulnerable and was scored by the computer as one of the factors increasing the probability of contracting sili-

cosis. In the USSR, men under 20 are not admitted to underground work, as well as women of any age. Our mathematical prognosis shows that introducing these two employment restrictions into other industries with a high risk of silicosis could reduce morbidity approximately 50%. This is a good illustration of the potential of collective biological prophylaxis.

## Possibilities of a Genotype Selection

Much more complicated than showing effects of sex and of age at beginning the "dusty" work is revealing any really individual biologic feature that could be used as an index prognostic of silicosis and, thus, give ground to a medical recommendation to avoid such a work. In particular, we touched on the problem of the genetic predisposition to pneumoconiosis in our previous review (2), and our conclusions based on the analysis of literature data were far from optimistic. We stressed, for example, that when comparing pneumoconiosis patients with healthy persons, different investigators (4-17) revealed up to 15 HLA antigens having different prevalence in ill and healthy groups; however, practically none of these results proved reproducible (Table 1).

We feel that such an approach to the search of a genetic marker of predisposition to silicosis has two serious shortcomings. First, it does not consider that patterns of sensitivity or of resistance to agents causing a disease depend, as a rule, not on a single gene but on the complete phenotypic complex (18). Therefore, a multifactorial analysis of correlations between this complex and the probability of a disease should be chosen rather than a simple monofactorial case-control study.

Table 1. HLA antigens and pneumoconiosis according to different author's data.

Kind of pneumoconiosis	Antigens detected	Type of correlation with the disease <sup>a</sup>	Reference
Asbestosis	B27	Positive	(4)
Asbestosis	B12	Positive	
	B5	Negative	
Silicosis	B7	Negative	(6)
Asbestosis	B27	Positive	(7)
Asbestosis	B8	Positive	(8)
Silicosis	B8, B13	Positive	(9)
Asbestosis	B27	Positive	(10)
Asbestosis	B18, B27, C2	Negative	(11)
Coal miner's pneumoconiosis	A1	Negative	(12)
Coal miner's pneumoconiosis	B6, B7, B22, B13	Negative	(13)
	C5	Positive	
Coal miner's pneumoconiosis	—	No correlation	(14)
Asbestosis	—	No correlation	(15)
Silicosis	A19, B18	Positive	(16)
Silicosis	B10	Negative	(17)

<sup>a</sup>"Positive" or "Negative" means that the prevalence of this HLA antigen was found in the case group statistically significantly higher or, respectively, lower than in the control group of the corresponding investigation.

Second, although the latter type of study, as a rule, used matched controls, the compared groups in the investigations referred to were usually equalized only with respect to age and sex. Meanwhile, we know now that quite a number of other features can also be of great importance as factors influencing the susceptibility to silicosis (2,3). When one studies small population samples, random intergroup differences regarding these features are practically inevitable. If they are considered, such differences can either conceal or simulate the role of genotypic distinction under research.

Because of these considerations we used, for the analysis of the role played by HLA antigens in the susceptibility to silicosis of employees of the same silica firebrick factory, the pattern recognition method previously used for resolving other problems in this field. Each of 40 cases of simple silicosis was matched with two controls with respect to their job, chronic bronchitis and/or rheumatism, age at beginning of dust exposure, sex, and nationality. Each of 39 cases of silicotuberculosis was also matched with two controls with respect to their job, chronic bronchitis and/or pneumonia (in the anamnesis), sex and nationality. These criteria of matching controls were chosen taking into consideration the degree of influence of corresponding features on the development of silicosis (silicotuberculosis) in workers at that factory, as shown previously (3), or their relation to genotype. Such an interfering interrelationship should be eliminated as far as possible in order to estimate prognostic value of the special genetic marker under investigation. Regarding other previously established factors, both biological and environmental, also influencing the probability of contracting silicosis or silicotuberculosis, it is important to mention that intergroup differences of their average value or prevalence were quite negligible.

In the blood of all 237 workers, 39 antigens of the HLA system loci A and B were determined, but only 26 of them were detected. Of each cohort 15% were used as control samples for a verification of the reliability of the distinction rule elaborated by the computer when learning to recognize the patterns of the remaining 85%. This verification gave the following results: In regard to simple silicosis, the individuals who had contracted this disease were recognized correctly in 75% of the cases; those who had not contracted the disease were recognized in 100% (in regard to silicotuberculosis in 100% and 75%, respectively). Thus, the correlation between genotype as determined with investigated HLA antigens and individual susceptibility to silicosis or silicotuberculosis, although not absolute, still could be demonstrated quite distinctly.

In Table 2, 10 HLA antigens are listed in the order of decrease of their informativeness regarding recognition of silicotic versus silicotuberculous pattern. While the informativeness of the first antigen of such a sequence equals 1.0 (in arbitrary units), that of the last one equals but 0.04 for simple silicosis and 0.12 for silicotuberculosis. It is quite evident that dependence on HLA-genotype is not the same for these two variants of pneumoconiosis. For example, the A3 antigen was the most informative for the recognition of predisposition to silicotuber-

Table 2. HLA antigens predetermining susceptibility to silicosis or to silicotuberculosis in the order of decreasing informativeness.

Place in the order	For simple silicosis		For silicotuberculosis	
	Antigen	Type of correlation <sup>a</sup>	Antigen	Type of correlation
1	B8	-	A3	+
2	B12	-	B13	+
3	A10	+	A11	-
4	A2	-	A19	-
5	A11	+	B7	+
6	B22	+	B8	+
7	B40	+	A2	+
8	A9	+	A9	-
9	A19	-	B22	+
10	B15	+	A1	+
11	B13	+	B18	-
12	B7	-	B21	+
13	A1	-	B40	+
14	B16	-	A28	-
15	B17	+	B5	-
16	B35	+	B14	-
17	B21	+	B16	-
18	B38	+	B27	-
19	B5	+	A10	-
20	B27	+	B15	+
21	A3	-	B35	+
22	B14	-	B12	+
23	A16	-	A16	-
24	A23	-	A23	-
25	B18	-	A32	-
26	A28	-		

<sup>a</sup>(+) shows that individuals possessing these HLA antigens are predisposed; (-) shows that those possessing these HLA antigens are resistant to development of silicosis.

culosis (i.e., it increased the probability of contracting the disease); but it attained only the 21st place of informativeness regarding the susceptibility to simple silicosis, this susceptibility being, on the contrary, lower for individuals having this antigen.

Dermatoglyphic characteristics of an individual, genetic markers that can be determined much easier and less expensively as compared with HLA antigens, are of even greater interest in the light of the eventual practical task of screening applicants for employment in hazardous industrial environment according to their susceptibility or resistance to the specific injurious exposure. It is known that there are dermatoglyphic features typical of some hereditary diseases or of predisposition to some non-hereditary ones (19-21). In order to elucidate whether there are similar correlations of dermatoglyphs with susceptibility to silicosis and/or silicotuberculosis, we adopted the same methodology of multifactorial analysis along with matching cases with controls with respect to the most relevant individual characteristics.

The investigation was conducted at the factories producing silica or aluminosilicate firebricks. To illustrate the results, we shall use data concerning the silica firebrick factory, where 46 cases of simple silicosis and 49 cases of silicotuberculosis with matched controls (one for each case) constituted the groups equalized as to features most influencing development of respective diseases. The criteria of matching were the same as those described previously.

In the test samples of all groups (i.e., on the individuals whose data have not been used for teaching the computer) 100% of the cases and controls were recognized

correctly as those who would or would not contract silicosis or silicotuberculosis. When the number of dermatoglyphic characteristics were reduced from the originally used 59 (22) to those 10 that proved most informative, the reliability of pattern recognition did not become much worse; thus, in controls to cases of simple silicosis the proportion of correct recognitions decreased to 80%, while in three remaining groups it still was 100%.

The results presented in Table 3 clearly demonstrate once more that genotypes predisposing to silicosis or to silicotuberculosis are essentially different. It is true not only in regard to the order of informativeness of the dermatoglyphic features but to their meaning as well. As it was shown concerning the prognostic significance of the HLA antigens, there are also some dermatoglyphic features that favor (or hinder) development of both simple silicosis and silicotuberculosis. For example, ridge count of the left palm indicates an increased probability of contracting either the former or the latter form of pneumoconiosis when it does not exceed 35, and decreases this probability when it is greater than 35. There are, however, many examples of opposite influence of a feature on silicosis versus silicotuberculosis development. Thus, the number of palm lines less than 5 appears to be a feature increasing the probability of disease as concerns simple silicosis and decreases this probability when it exceeds 5, whereas in silicotuberculosis both features have the opposite meaning.

Evidently, it is no mere chance that in a big proportion of silicotuberculosis cases this disease is being discovered as such from the very beginning (i.e., circumventing the stage of perceptible simple silicosis) even in those work-

**Table 3. The 10 most informative dermatoglyphic characteristics predetermining susceptibility to silicosis or to silicotuberculosis in the order of decreasing informativeness.**

Place in the order	For simple silicosis	For silicotuberculosis
1	Ridge count of 3rd finger, the left hand	Width of the right palm lines
2	Ridge count of 5th finger, the left hand	Ridge count of the left palm
3	Ridge count of 2nd finger, the right hand	Position of the right palm axial triradius
4	Total ridge count of left hand fingers	Ridge count of 3rd finger, the left hand
5	Ridge count of 2nd finger, the left hand	Type of the interdigital pattern between 3rd and 4th fingers, the right hand
6	Total ridge count of fingers of both hands	Dysplasia of left palm ridges
7	Number of palm lines on the right hand	Type of pattern on the 2nd finger, the right hand
8	Total ridge count of right hand fingers	Type of pattern on the 3rd finger, the right hand
9	Number of palm lines on left hand	Type of pattern on the 1st finger, the right hand
10	Ridge count of 5th finger, the right hand	Ridge count of the right palm

ing populations that are subject to annual qualified medical examinations with X-ray investigation, thus the probability of that stage having been overlooked earlier by physicians is low enough. The population under discussion is one of those.

When an identical investigation was conducted at aluminosilicate-firebrick factory, the results of pattern recognition were no less reliable. However, the combination of dermatoglyphic features predisposing to simple silicosis was quite different from the respective combination found in the silica-firebrick plant, while as far as silicotuberculosis goes, the discrimination rules elaborated by the computer for the both working populations were very similar. The reasons for such poor reproducibility of the dermatoglyphic pattern of predisposition to simple silicosis demand further elucidation, but the real existence of a certain genotype predisposing to silicotuberculosis and permitting prediction of an increased risk of this most dangerous of all forms of pneumoconioses has been revealed rather convincingly.

It seems logical to suppose that in fact we deal with genetic predisposition to tuberculosis that can be manifested with the highest probability just under silica dust exposure, the manifestation being that form of a combined disease that is called silicotuberculosis. Let us specify that only those cases of silicotuberculosis that had been revealed as such from the very beginning, and only those of simple silicosis that had remained uncomplicated with tuberculosis up to the moment of our investigation (which was conducted up to 25 years after receiving the diagnosis), were included in the above-mentioned groups for teaching the computer. However, after the discrimi-

nation rule had been elaborated on those groups, the computer could recognize as silicotuberculous also most of the cases that had been primarily diagnosed as simple silicosis and only later complicated with tuberculosis. In other words, the assumed genetic predisposition to tuberculosis manifests itself on the background of silica accumulation in lungs either through primary development of silicotuberculosis or through a particular tendency to secondary tuberculous complication of primary simple silicosis.

When the computer was given the dermatoglyphic characteristics of 35 citizens of the same town that had never been occupationally exposed to dust but were ill with pulmonary tuberculosis, it recognized 75% of these cases as ill with silicotuberculosis. If we take into account that this group had not been specially equalized with respect to any relevant feature with groups of the silica-brick factory employees which were used for the elaboration of discrimination rule, then such a high percentage of correct recognitions appears rather meaningful. It gives support to the previously mentioned hypothesis according to which the same genetic predisposition that favors development of common tuberculosis in persons never exposed to silica dust makes them susceptible to silicotuberculosis development if they are placed (in this experiment quasi-placed) under dust exposure.

Our institute has positive experience of using the BCG vaccination or antimycobacterial drugs for tuberculosis and silicotuberculosis prophylaxis in some "dusty" industries (23).

## Autonomic Nervous System and Selection of Silica-Resistant Individuals

If the level of silica dust exposure is set, the higher or lower probability of contracting silicosis depends considerably on individual efficiency of natural mechanisms of pulmonary dust clearance, especially of silica particle elimination from the alveolar region. Although the individual clearance efficiency was quantitatively estimated by many investigators in a lot of experiments on volunteers inhaling labelled aerosols, such a test might not be feasible for purposes of large-scale occupational screening and/or recommendation.

It is well known that silica dust exerts an especially damaging influence on the main mechanism of alveolar clearance, i.e., on the macrophage phagocytosis of particles, being highly cytotoxic for macrophages. Experimental data that demonstrate that this damage is partly compensated by enhanced contribution of neutrophil leukocytes to phagocytosis of cytotoxic particles and, thus, to their clearance from lungs, have been summarized previously (24). Later it was shown that the role of this compensatory mechanism became still more important under long-term quartz dust inhalation exposure (25). When the development of silicosis in lungs of exposed rats reached a certain level, the macrophage mechanism of phagocytosis became so grossly damaged that the dif-

ference between bronchoalveolar lavage (BAL) macrophage counts of exposed and control rats, quite considerable at early stages of the experiment, completely disappeared. Meanwhile, the respective difference in the BAL neutrophil leukocyte counts continued to increase steadily. One could hardly find another feasible explanation of the paradoxical maintenance of the original high clearance rate both during and after the exposure period in this experiment, the complete failure of the macrophage mechanism of this clearance notwithstanding.

Thus, some doubts are justified as to the predictive value of estimating the clearance efficiency before occupational exposure has begun (still less, of estimating it by means of a single and very low exposure to noncytotoxic particles of labeled test aerosols) for prognosis of an individual's resistance to long-term silica dust exposure. Rather, one could use for such a prognosis two other estimates. The first of them, namely, an estimate of a person's macrophages' sensitivity to quartz cytotoxicity, has already been proposed (2), but still needs methodical elaboration. As to the second estimate, it should give a criterion permitting prediction of a more or less efficient contribution of the neutrophil leukocyte phagocytosis mechanism of pulmonary dust clearance in response to the macrophage damage.

The factor controlling this compensatory mechanism is the quantity of products of macrophage breakdown (PMB), which are produced by cytotoxic particles action and operate either directly (24), or through the activation of viable alveolar macrophage releasing a neutrophil attractant (25). It was shown, however, that in response to a fixed dose of the PMB the host might recruit into alveoli substantially different numbers of neutrophil leukocytes depending on its neurohormonal status (24,26,27). In particular, this recruitment is favored by previously injected M-cholinomimetic or  $\alpha$ -adrenoblocking drugs and hindered by M-cholinolytic or sympathomimetic ones. It seems reasonable to expect that some natural predominance of the parasympathic tonus should be favorable for involving the compensatory mechanism under consideration (and thus give ground for predicting a higher resistance to silica dust pulmonary retention), whereas predominance of the sympathetic tonus creates a worse condition for this involvement, even as compared with a relatively balanced type of autonomic neuroregulation.

We have conducted a case-control study comparing workers of the silica-firebrick factory who had contracted silicosis or silicotuberculosis with those who had not, using a special methodology of estimating the status of autonomic nervous system based on a large number of functional indices (28). It was found that the prevalence of persons with different types of this status corroborated our expectations. Indeed, in the group of silicotic and silicotuberculous patients, there were more individuals with a clear predominance of the sympathetic tonus, whereas in the group of those who had neither of these conditions the individuals with a clear predominance of the parasympathic tonus prevailed.

In contrast to genotype, this feature did not reveal any significant difference between patterns of predisposition

to silicosis or to silicotuberculosis. It was not unexpected, for as far as the latter depends on accumulation of dust in pulmonary tissue of persons with predisposition to tuberculosis. Anything leading to a lesser efficiency of pulmonary self-clearance should promote the development of silicotuberculosis just in the same manner as it promotes that of simple silicosis in persons without such predisposition. Thus, we might combine all patients in a group. In this group, there were 70% of markedly sympathotonic persons, while in the control group, only 36% ( $p < 0.05$ ). As to markedly parasympathotonic individuals, their prevalence in the same groups was 10% and 37%, respectively ( $p < 0.05$ ).

Meanwhile, there were no statistically significant inter-group differences concerning the proportion of individuals without a clear predominance of sympathetic or parasympathic influences (presumably those with a balanced type of autonomic nervous system). There were 20% such "in-betweens" in the silicotic group and 27% in the control.

When a clear predominance of sympathetic tonus is revealed along with an unfavorable genotype as detected by means of HLA antigens or, even better, by means of dermatoglyphs, medical advice to such a person to avoid occupations connected with silica dust exposure seems to be most justified.

## Individual Biological Prophylaxis: Avoiding Unfavorable Influences

Though many people would rather take daily some "prophylactic pills" than give up their harmful habits or exclude anything from their traditional food, it is just such measures one should recommend first of all when considering possible means of enhancing a host's resistance to the injurious effects of silica dust.

Smoking and overindulgence in alcohol always appear in our investigations as factors decreasing that resistance. Wherever the multifactorial analysis was conducted (in copper mines, in silica-firebrick, or in aluminosilicate-firebrick factories), the development of both simple silicosis and silicotuberculosis was found to be promoted by these two harmful habits. Moreover, one has to take into account that among other factors promoting development of simple silicosis, chronic bronchitis is one of the most important (2,3). It is well known that this condition, in its turn, depends to a large degree on smoking. Meantime, even without excluding chronic bronchitis from an individual's set of relevant features but only substituting in all silicosis cases the characteristic "non-smoker" for the real characteristic "smoker" (whenever the latter was true), the computer answered: "this person has no silicosis" in 9 to 14% of the cases which without such substitution have been correctly recognized as silicotics.

A similar experiment on the mathematical model has shown that without an overindulgence in alcohol the prevalence of silicosis in our cohorts would still be 10 to 13% less. If one takes into account that the discrimina-

tion rules were elaborated on cohorts in which "nonoverindulgence" did not, in most cases, imply a teetotaler, it is easy to understand that a wide and considerable reduction in strong liquor consumption, apart from its other well-known medical, biological, and social advantages, might bring on a quite considerable reduction of silicosis morbidity.

Moving on to the planning of rational diets, we also like to point out first of all what should be avoided. The problem of nutritional factors of susceptibility to silicosis has already been discussed (2). Specifically, we referred to many experiments that had confirmed repeatedly that an excess fat load, especially with fats that have a high content of unsaturated fatty acids, enhances cytotoxicity and fibrogenicity of quartz (29-34). The only epidemiological study known to us as testifying to more rapid development of silicosis in miners consuming a considerable quantity of pork fat in their diets was also mentioned (2). However, if the fat load that enhances silicotic fibrogenesis in rats not exposed to any other influences was given to those that performed daily running on a treadmill, not only was that enhancement not observed, but it was shown that the excess fat prevented an increase of silicosis severity caused by hard muscular exercise in rats not given additional fat (31,32).

The role of the fatty acids unsaturation was clearly demonstrated in our further experiments with the *per os* administration to rats of Linetol, a preparation of mixed fatty acid esters extracted from linseed oil (34). The iodine number of this mixture exceeds 166, whereas that of sunflower oil (which in the previous experiments proved to be a more potent promoter of silicotic fibrogenesis as compared with animal fats) is approximately 130. Rats that had been instilled intratracheally (IT) with 50 mg standard quartz DQ<sub>12</sub> in/or 1 mL normal saline were then being given through gastric tube either of those two oils in a dose of 10 g/g body weight/week, this additional fat load being equal to approximately 40% of their diet fat content. Two months after the IT instillation, the pulmonary hydroxyproline content in control rats was  $3681 \pm 335 \mu\text{g}$ ; in rats administered quartz dust and then given sunflower oil,  $23871 \pm 1946 \mu\text{g}$ ; and in those administered quartz and then given Linetol,  $37649 \pm 5937 \mu\text{g}$  (all differences are statistically significant). In the latter group the lipid peroxidation rate, as estimated with accumulation in the pulmonary tissue of both malondialdehyde and conjugated dienes, was also the highest.

Within the scope of this paper we are not allowed to enter in more details of theoretical considerations and experimental data concerning the essential, although most probably not the principal, part taken by lipid peroxidation as a mechanism of silica cytotoxicity and, thereby, of its fibrogenicity (36-39). If we acknowledge this, however, we can easily understand the unfavorable influence of fatty acids with high iodine numbers. The type of alimentary fats affect the saturated to unsaturated phospholipid ratio in lipoprotein membranes of the cell, and if increasing unsaturation of the phospholipids, it makes these membranes more sensitive to the injurious action of lipid peroxidation and, thus, of silica particles.

Therefore, the recommendation not only to avoid an excess of any fat in the diet of workers exposed to silica dust (and more so, in the diet of silicotic patients) but first, to restrict reasonably the quota of fats with a high degree of unsaturation, would be justified. However, it is easily seen that this recommendation is in contradiction with generally accepted views on the favorable role of such unsaturated fats in prophylaxis of some other diseases (e.g., atherosclerosis). Finding the golden mean needs special investigation.

It does not appear necessary to limit total fat in the diet of those workers whose silicosis-inducing labor requires hard muscular work. However, even for these workers, restricting unsaturated fatty acid content in alimentary fats would be useful.

## Favorable Influences: Lifestyle

The favorable influence of a healthy lifestyle on the host's resistance to a wide variety of diseases is not likely to arouse any doubts. Nevertheless, one should ask if there is any evidence for a definite statement that some or other positive factor usually included in the concept of a healthy lifestyle could really enhance the host's resistance to injurious effects of the particular harmful agent under consideration, i.e., of silica dust.

There is an indication that pneumoconiosis prevalence in miners who were engaged in any sport activity was lower in contrast to those who were not (40), but thoroughness of the epidemiological analysis was not quite satisfactory. As to animal experiments, they certainly do not give a very adequate model of human sporting exercise. However, it is interesting that while heavy muscular training of rats exposed to quartz dust inhalations (separately from this training) enhanced, as mentioned earlier, silicosis development, in a similar experiment with the treadmill speed half as high as in the previous one we observed a beneficial effect of increased alveolar macrophage resistance to silica particle cytotoxicity along with some attenuation of silicotic pulmonary fibrosis (41). Therefore, it might be assumed that participation in popular sports with moderate muscular exertions would really favor a more or less considerable decrease of the prevalence of silicosis in working populations.

A hypothetical mechanism of such a favorable influence of various factors of the nonspecific adaptation on host resistance to different injurious agents have already been discussed (2). In the same overview we proposed an explanation of the fact that cold acclimatization of rats, even to moderate and short-term intermittent cooling, always enhanced silica dust retention and pulmonary silicosis development in spite of an increase of alveolar macrophage resistance to silica cytotoxicity. However, an extrapolation of these results to human practice would be even less reliable taking into consideration the substantial difference of cold acclimatization mechanisms in man and in rodents.

There is not doubt that in man a gradual adaptation to cooling (what is in Russian quite appropriately named



"steeling" of organism) increases its resistance to common cold and, hence, decreases the probability of contracting pneumonia or acute (and then chronic) bronchitis. Meantime, as stated earlier, these diseases rank high in the list of factors increasing individual susceptibility to silicosis. Therefore we feel that such "steeling," e.g., winter sports, should be included in medical recommendations aiming at biological prophylaxis of silicosis.

## Nutritional Factors and Food Additives

Among 12 individual features that *in toto* permitted prediction with high reliability whether a miner would or would not contract silicosis, the 7th place in decreasing order of informativeness was the possession of a garden, a kitchen garden, and, in some cases, of a cow and/or poultry (2). It may be considered as circumstantial evidence in support of a favorable influence of sound nutrition comprising fresh farm products (milk, vegetables, fruit) in a higher-than-usual proportion. (At the same time, we should not forget that outdoor muscular activity and possibility of repose in such a natural environment represent important aspects of healthy lifestyle in general.) Prophylactic value of balanced and high-grade diet follows from the general concept of dependence of susceptibility to silicosis on the host's reactivity and nonspecific resistance (2). There are not, however, as far as we know, any direct epidemiological data proving this value.

The same must be said about the protective role of vitamins. As to experimental data concerning the influence of vitamins on the development of silicosis, they are scarce and not always convincing. In one of the experiments in our laboratory, it was found that a polyvitaminic preparation given to rats daily enhanced the severity of silicotic pulmonary fibrosis (34). One may suppose that such a result was due to a vitamin overdose, especially to an excess of ascorbic acid, which is known to be a necessary component of the enzyme system controlling the biosynthesis of collagen (42). There are enough experimental data (43) demonstrating an increased ascorbic acid content of pulmonary tissue in silicotic rats, and the additional administration of this vitamin to rats enhances both this content and development of silicosis (44).

The role of lipid peroxidation in silicosis points to the expediency of prophylactic administration of vitamin E. A negative result of the first published experimental attempt to inhibit silicotic fibrogenesis with  $\alpha$ -tocopherol administration (45) was due, in our opinion, to the author's having not taken into account prosilicotic effect of the oil vehicle, which constituted a quite considerable additional fat load to rat. Indeed, as it was shown later (46), the equivalent dosage of sunflower oil when administered *per os* to rats instilled IT with quartz dust noticeably enhanced development of silicosis, while tocopherol precluded completely this synergistic effect of the oil administered together with the vitamin. It was also found in the same investigation that  $\alpha$ -tocopherol increased antisilicotic action of another antioxidant,

namely, sodium selenite.

Later it was demonstrated that on the background of long-term quartz dust inhalation exposure, the combination of tocopherol with selenite also induced several beneficial changes as compared with rats exposed to the same dust without any medication and especially with those given oil without antioxidants. The lipid peroxidation level in pulmonary tissue decreased while its antioxidant activity increased; dust-induced shifts in the BAL cell population reflecting cytotoxicity of particles were significantly less pronounced; silicotic fibrosis development was partly inhibited (39). It was shown as well that peritoneal macrophages taken from rats given the same oil solution of  $\alpha$ -tocopherol during some preceding period were more resistant to both prooxidant and cytotoxic action of silica particles *in vitro* than macrophages from rats given only oil (47). Apparently it would be justified to use with prophylactic purposes also some other vitamins possessing antioxidant properties (e.g., A and B<sub>6</sub>).

However, working out comprehensive recommendations for the rational prophylactic nutrition of workers at risk to silicosis is far from being accomplished, and it certainly is one of the most urgent tasks in the problem of biological prophylaxis of the disease. We are placing such emphasis on the significance of antioxidant vitamins only because the unfavorable role of enhanced lipid peroxidation in silicosis pathogenesis appears above any doubt. It is well known that improper nutrition regarding preventing excessive lipid peroxidation is very typical of developed countries in general. However, the role of other components of food, first of all, of proteins (with respect to both their total quantity and composition) needs further study.

Sodium glutamate, which is now one of most widely used food additives, was shown to be a potent protector of an organism against cytotoxic and, thereby, fibrogenic, action of dust, especially of the silica dust. As experimental results demonstrating this protective action and substantiating certain hypotheses concerning its mechanisms were published in English and German (48-50) and thus are easily accessible to western scientists, we shall confine ourselves to an illustration of some results of one of many experiments that had been conducted to estimate that action (Table 4).

In rats allowed to drink 1.5% solution of sodium glutamate instead of water on the background of long-term quartz dust inhalation exposure, not only were the shifts of the BAL cell population reflecting cytotoxic effect of deposited particles markedly reduced, but so were all usual effects of the pulmonary macrophage breakdown caused by silica particles, i.e., dust retention in lungs and even more so in tracheobronchial lymph nodes and development of pulmonary silicosis as judged from increase of lung weight and their lipid and hydroxyproline content. A quite similar protective effect of glutamate was observed in rats killed after 3 months of exposure.

Later it was shown that an increased resistance to standard quartz cytotoxicity *in vitro* of peritoneal macrophages taken from rats that had been drinking sodium glutamate solution was essentially the same regardless



Table 4. Main characteristics of rats exposed to quartz dust or given glutamate solution to drink.<sup>a</sup>

Measurement	Exposure			
	Control	Glutamate	Quartz	Quartz and glutamate
Bronchoalveolar lavage				
Total no. of cells, $\times 10^6$	6.98 $\pm$ 1.12	5.57 $\pm$ 0.64	9.61 $\pm$ 0.56*	6.30 $\pm$ 0.93**
NL/AM ratio <sup>b</sup>	0.12 $\pm$ 0.02	0.09 $\pm$ 0.02	0.44 $\pm$ 0.02†	0.31 $\pm$ 0.04**
% Clearly degenerated AM	17.2 $\pm$ 2.0	10.9 $\pm$ 1.4*	45.2 $\pm$ 3.3‡	10.2 $\pm$ 0.9††
Lungs				
Dry weight, mg	403.5 $\pm$ 13.4	346.0 $\pm$ 11.1†	635.7 $\pm$ 31.0‡	511.9 $\pm$ 21.1**
Dust content, mg <sup>c</sup>	2.3 $\pm$ 0.4	0.8 $\pm$ 0.2†	16.0 $\pm$ 1.8‡	5.8 $\pm$ 0.5††
Hydroxyproline content, $\mu$ g	5310 $\pm$ 189	4442 $\pm$ 154†	7165 $\pm$ 369‡	5307 $\pm$ 315††
Lipid content, mg	55.2 $\pm$ 3.6	51.8 $\pm$ 2.7	125.3 $\pm$ 10.5‡	85.5 $\pm$ 8.7**
Lymph nodes				
Wet weight, mg	132.5 $\pm$ 15.3	124.6 $\pm$ 12.6	315.8 $\pm$ 23.8‡	193.1 $\pm$ 23.3††
Dust content, mg <sup>c,d</sup>	0.24	0.05	2.22	0.51
Hydroxyproline content, $\mu$ g <sup>d</sup>	144	No data	448	300

<sup>a</sup>Values are means  $\pm$  SE.<sup>b</sup>NL, neutrophil leukocytes; AM, alveolar macrophages.<sup>c</sup>Dust content of lungs and lymph nodes was estimated as the acid-insoluble ash residue.<sup>d</sup>Dust and hydroxyproline content in lymph nodes were determined in pooled tissue samples, which precluded the estimations of SEs of means.\*Significantly different from control,  $p < 0.05$ .†Significantly different from control,  $p < 0.01$ .‡Significantly different from control,  $p < 0.001$ .\*\*Significantly different from quartz exposure group,  $p < 0.01$ .††Significantly different from quartz exposure group,  $p < 0.001$ .

of whether its concentration was 1.5% or 0.5% (51). It was shown as well that the protective effect persisted a rather long time after glutamate administration had been terminated and then gradually dies away. Based on these data and taking into consideration that calculation of effective doses of this biologically active metabolite for humans should be based not on man-to-animal body weight ratio but rather on their basal metabolisms or daily protein consumptions, we would recommend for prophylactic and therapeutic purposes a daily dose of about 2.0 g given during 2 to 3 months with intervals between such courses of treatment not exceeding 6 to 8 months every year. A long-term experiment on volunteers to assess the prophylactic effect of such a treatment is being conducted in our institute by A. A. Toropov, and its preliminary results are satisfactory.

As a membrane-stabilizing (including anti-silica) effect of glutamate can be related to its active participation in the energy metabolism of a cell with accumulation of excessive energy as ATP, some other substances participating in the tricarboxylic acid cycle were also tested as possible anti-silica protectors (52,53). As could be expected, malate proved no less an effective protector than glutamate for both isolated mitochondria and peritoneal macrophages *in vitro*. Succinate, while being far less effective by itself, exerts some degree of synergism with glutamate. Thus, perspectives of search for new active metabolites and their combinations that could take part in biological prophylaxis of silicosis are not yet closed.

## Some Biological Aspects of Controlling Cumulative Dust Exposure

In order to decrease the risk of an occupational disease, the organized time restriction of a single or of a total long-

term exposure to a harmful environmental factor is frequently used. As far as the prophylaxis of silicosis is concerned, the most usual criterion of such defense with time factor is the cumulative dust exposure (CDE), which is the sum of products of multiplication of dust concentrations to which a worker was ever exposed during all his working period by durations of respective exposures (54). Thus, the complete termination of occupational dust exposures can be recommended, but only after the CDE attained some fixed level, its danger having been previously established by epidemiologic studies.

Even without any direct control of the CDE, in our country, miners and workers of some other occupations with a high risk of silicosis enjoy a right to receive a pension and may retire completely 10 years earlier than the general population. Thus, here one also could say that dust exposure is shortened but after adding up to a complete CDE. However, along with such final restrictions of the total working period, the same workers enjoy other forms of defense with time factor: namely, their working shift is shorter than in safer industries or social service, and their yearly paid vacation is longer. (The very same protective and compensatory measures are in force for many other occupations connected with some or other potentially harmful exposure.)

The problem of comparative efficiency of different methods of the CDE restriction boils down to the question how, if at all, the harmful effect of a fixed dose of dust depends on its time distribution pattern and, thus, is biological in its essence. A special mathematical analysis (55) and a long-term inhalation experiment corroborating its conclusions (25,56) demonstrated that such a dependence really exists. As concerns prophylactic efficiency of the defense with time factor against silicosis, those conclusions are briefly as follows.

First, the nearer to the finish of the total working period a time interval void of dust exposure is shifted, the

less effective is the restriction of the CDE. The least prophylactic effect can be obtained just breaking dust exposures after the maximal allowable CDE has already been reached; the biggest effect is seen with corresponding shift of the beginning of dust exposure to more advanced age.

Second, if the total exposure (working) period is divided into a number of equal subperiods, each concluded with the same nonexposure interval, then at a fixed CDE, the higher that number, the lesser the degree of silicosis at the end of period. In other words, an additional yearly vacation appears to be more effective compared with breaking dust exposure once by corresponding total shortening of that period in the very end of it.

It is understandable that the choice of one or another form of realization of the defense with time factor principles depends to a large extent on technological, social, and economic factors. However, when these factors have been taken into account, it should be wise to consider the results described as well and, whenever possible, to choose the variant of such defense that is most effective biologically.

## Conclusion

Both theoretical premises and available experimental data, as well as the analysis of dependence of silicosis and/or silicotuberculosis on various genetic, acquired, and environmental characteristics of an individual, testify for the statement that biological prophylaxis of those diseases (as a supplement to engineering means of dust control) might be rather effective. It needs not only further investigations but also practical use and evaluation of some recommendations that are already well substantiated.

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